UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/064,057	04/22/1998	GARY F. GERARD	0942.4330002	5386

26111 7590 10/25/2004

STERNE, KESSLER, GOLDSTEIN & FOX PLLC
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20005

EXAMINER	
NASHED, NASHAAT T	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 10/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/064,057	GERARD ET AL.	
	Examiner	Art Unit	
	Nashaat T. Nashed, Ph. D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 September 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26,33,117-125,137-147 and 149-161* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26, 33, 117-125, 137-147, and 149-161* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 2, 2004 has been entered.

Claims 26, 33, 117-125, 137-147, and 149-161 are pending and under consideration in this Office action.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 26, 33, 117, 122-125, 137-147, and 149-161 are rejected under 35 U.S.C. 103 as being unpatentable over Soltis *et al.* in view of the state of the art at the time of the application was filed as exemplified by Kawa *et al.* (IDS Reference), Barr *et al.* (IDS Reference), and Ford et al. (Prot. Expr. Purif. 1991, 2, 95-107), for the reasons set forth in the prior Office actions mailed January 2, 2004 and March 21, 2003.

Soltis *et al.* teach the expression separately of both the α- and β-subunits of AMV-reverse transcriptase in *E. coli* host cell. They teach that the isolated α- and β-subunits have a reverse transcriptase and function as homodimers, see abstract. They teach the construction of pRC23-p95 for α-subunit and pRC23-p63 for β-subunit, see page 3372, right column, last two paragraphs, the purification and assay for the enzyme, see page 3373, right column.

Kawa *et al.* teach the expression and purification of HIV-1 reverse transcriptase using baculovirus expression system (BVES) as the homodimer of the p66 which is not the mature p55/p66 heterodimer form of the enzyme, see abstract. Also, they teach that BVES would allow the expression of HIV-1 reverse transcriptase cDNA in eukaryotic cells, thereby taking advantage of the pathways in these cells that facilitate folding, modification, and assembly of protein products, see the paragraph bridging the two columns on page 302.

Barr *et al.* teach the expression of HIV reverse transcriptase in *Saccaromyces cerevisia* (yeast), see abstract. Also, they teach the expression of HIV reverse

transcriptase in yeast is efficient, and leads appropriately post-translationally modified protein, see the paragraph bridging the two columns on page 486.

Ford et al. review the prior art of the fusion tails used for the recovery and purification of recombinant proteins that included glutathione-S-transferase (GST), *E. coli* maltose binding protein (MBP) and polyHis-tags, see Table 1. Also, they teach immobilized metal affinity chromatography using various metal ions for isolating polypeptide comprising the His-tags. In addition, they teach that fusion tails have been added to both the N- and/or C-termini of the same protein in order to isolate extremely sensitive peptide.

AMV-reverse transcriptase has been used extensively in biotechnology in the preparation of cDNA libraries. Thus, one of ordinary skill in the art would have had motivation at the time of invention to develop a method to produce AMV-reverse transcriptase by a recombinant method. Also, the ordinary skill in the art would have been motivated to use eukaryotic host cell to produce the AMV-reverse transcriptase by the teachings of Kawa *et al.* and Barr *et al.* Thus, the ordinary skill in the art would have constructed a BVES or yeast vector as taught by either Kawa *et al.* or Barr *et al.* comprising the nucleic acid sequence encoding the α- and β-subunits of AMV-reverse transcriptase taught by Solies, transform a eukaryotic host cell with said vector, and culture the host cell as taught by Kawa *et al.* or Barr *et al.*, and purify the enzyme to any specific activity that suits his/here purposes, i. e., to any specific activity of any desired activity, by well known methods in the prior art (claim 26, 33, 117, 122-125, 137-147, and 149-161). The ordinary skill in the art would have been further motivated to coexpress the α- and β-subunits in the same host cell to produce the heterodimer because the heterodimer have higher thermalstability, see the abstract of Soltis *et al.* One of ordinary skill in the art would have been further motivated to express both subunits because the baculovirus system does not produce the heterodimer, which is taught Kawa *et al.* Thus, one of ordinary skill in the art would have been further motivated to construct a single vector comprising the coding sequences for both the α- and β-subunits of AMV-reverse transcriptase under the control of the same promoter which would lead to the production of equal amount of the two subunits. Alternatively, Ford *et al.* further motivate one of ordinary skill in the art to express both the α- and β-subunits units as fusion protein for easy purification. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made and was as a whole, clearly *prima facie* obvious.

In response to the above rejections of record, applicants continue to argue that Soltis *et al.* do not teach the claimed invention, and filed a declaration by Dr. Deb K. Chatterjce.

Applicants' arguments and Dr. Chatterjce declaration filed 9/10/04 have been fully considered, but they are not deemed persuasive. The claimed invention is directed to a recombinant method to make AMV-reverse transcriptase in eukaryotic cells. AMV-

reverse transcriptase is a commercial product, and crucial for making cDNA libraries. The nucleic acid encoding both the α- and β-subunits and their expression in bacterial cell such as *E. coli* are known in the prior art, see Soltis *et al.* Also, the expression of other retroviral reverse transcriptases such as that of HIV in eukaryotic cell is reported in the prior art, see Kawa *et al.* and Barr *et al.* Ford *et al.* teach the expression of polypeptides and proteins as fusion proteins and the purification of the fusion protein by affinity chromatography. The ordinary skill in the art would have been motivated to develop the claimed method because of the commercial value of the product of the method. The motivation to use eukaryotic cells in producing the AMV-reverse transcriptase is taught by both Kawa *et al.* and Barr *et al.* It should be noted that AMV is a virus that infects eukaryotic cells only, and as such the natural environment for producing the AMV enzyme is that of a eukaryotic cell. Finally, the expression of peptide/protein in host cell as a fusion protein and the purification of the expressed fusion protein by affinity chromatography have been a well-established technology in the prior art.

As indicated in the previous Office actions, the examiner agrees with the applicants that Soltis *et al.* do not teach the claimed invention, otherwise the rejection of the claims would have been made under 35 USC 102(b). The claims, however, are obvious over the prior art of record because the prior art provides one of ordinary skill in the art with the required teaching, motivation and expectation of success. It is said that the examiner fails to point to any specific disclosure in Kawa *et al.* or Barr *et al.* that teaches the enhanced specific and functional activity of the AMV-RT $\alpha\beta$ heterodimer produced by the method of the claimed invention. The AMV-RT $\alpha\beta$ heterodimer is the natural form of the reverse transcriptase and Soltis *et al.* teach that the heterodimer has higher thermal stability than the homodimer, which would have motivated the ordinary skill in the art to at the time of invention to co-express the two subunits to assure the production of the homodimer.

Applicants allege that they have obtained unexpected results and supported their alligation with a declaration by Dr. Chatterjce. In his declaration, Dr. Chatterjce discusses unexpected results obtained for the Rous Sarcoma Virus (RSV)-reverse transcriptase and not for the AMV-reverse transcriptase. The specification has no similar results for the AMV-reverse transcriptase, and no evidence to support applicants' position that similar unexpected results should be obtained in the case of the AMV-reverse transcriptase. To remedy this deficiency, Dr. Chatterjce argues:

> "Additionally, I have reviewed an Amino Acid Sequence Alignment Chart comprising the amino acid sequences of AMV-RT and RSV-RT (attached as exhibit C), as well as the literature upon which it is based. Based upon my understanding of the literature related to ASLV-RTs, it is my opinion that the chart is an accurate depiction of the amino acid sequences of both AMV-RT and RSV-RT. The data in

> the Amino Acid Sequence alignment Chart clearly show a conservation of over 95 percent of the amino acid sequence between AMV-RT and RSV-RT. Because AMV-RT and RSV-RT are from the same family of retroviral reverse transcriptaes (ASLV-RT) and have greater than 95 percent homology at the amino acid level, it is my opinion that one of ordinary skill in the art would understand that the results for specific and functional activities presented in the '057 application for RSV-RT could be extrapolated to, and therefore be representative of, the expected results for specific and functional activities in AMV-RT." The paragraph bridging pages 5 and 6.

It is clear from the testimony of Dr. Chatterjce that the RSV-RT and the AMV-RT are distinct chemical entities having different chemical structure, i.e., amino acid sequences. Extrapolating of unexplained and unexpected results to other chemical entities, be it from a closely related source, is not supported by the specification. RSV-RT and HIV-RT are closely related enzymes from lent virus and have substantial sequence homology, yet the specification teaches some subtle differences between two reverse transcriptases, and their behavior in host cells, see for example from line 15 on page 100 through line 6 on page 101; page 106, lines 23-25. Thus, there is no reason to believe that the AMV-RT would be expected to produce similar result to that obtained for RSV-RT. It should be noted that the specific activity of an enzyme preparation is a function of the degree of its purity as well as the history of the preparation. Without commenting on the validity of the data presented in Table 7, any enzyme preparation may be purified to any desired specific activity by one of ordinary skill in the art.

No claim is allowed.

This is a RCE of applicant's earlier Application No. 09/064,057. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is 571-272-0934. The examiner can normally be reached on MTTF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Nashaat T. Nashed, Ph. D.
Primary Examiner
Art Unit 1652